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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/068,751	11/02/1998	WOLFGANG-M. FRANZ	690-110PCT	2640

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EXAMINER	
SCHMIDT, MARY M	

ART UNIT	PAPER NUMBER
1635	25

DATE MAILED: 09/10/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/068,751	FRANZ ET AL.	
	Examiner	Art Unit	
	Mary Schmidt	1635	

-- The MAILING DATE of this communication appears on the cover sheet with th correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 June 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *52-73 and 76-82* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *52-73 and 76-82* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112

2. Claims 52-73 and 76-82 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for specific Ad-rsvLuc compositions exemplified in the specification, i.e. particular viral vectors having the significant regions of the adeno-viral vector and the mlc-2 promoter as to achieve the unexpected results over the prior art (such as the disclosed Buttrick et al. paper argued in the response received 12/4) and methods of administering such compounds via direct injection to the cardiac tissue discussed by Franz et al. (Cir. Res. 73 (4), p. 629-38), does not reasonably provide enablement for the scope of any viral containing mlc-2 composition claimed nor for expression via any route of administration as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims for the same reasons of record as set forth in the Official Action mailed 12/20/01.

Applicant's arguments filed June 20, 2002, have been fully considered but they are not persuasive.

New claims 63-82 are drawn to recombinant virus vectors according to claim 62, wherein said replication deficient adenovirus vector consists of two inverted repeat sequences (ITR) of said adenovirus; the recombinant virus vector according to claim 53, wherein said virus vector is an adenovirus vector or and adeno-associated virus vector; the recombinant virus vector according to claim 80, wherein said virus vector is a replication deficient adenovirus vector; and the recombinant virus vector according to claim 81, wherein the replication deficient adenovirus vector consists of two inverted terminal repeat sequences (ITR) of said adenovirus. The new claims do not further provide claims specific argued in the previous Official Action as being enabled to make and use for the unexpected cardiac muscle cell specific expression found in Applicant's specific vectors used.

In the Interview with Applicant on 11/16/01, unexpected results were discussed with respect to the previous 35 U.S.C. 103 rejection. Specifically, it was pointed out that it was the combination of the adenoviral vector used and the specific regions of the mlc-2 promoter which produced the successful cardiac-specific tissue expression of the disclosed constructs *in vivo*. Applicant reiterates this argument in the Amendment received 12/4/01 and an accompanying declaration which points out in section 5 (pages 2-3 of the declaration) the unpredictability of the combination of mlc promoters and viral vectors for cardiac-specific tissue expression in a somatic gene transfer *in vivo*.

Furthermore, in the declaration filed June 20, 2002, Applicant provides data showing the corresponding sequence of the human regions of the human mlc-2 gene that are equivalent to the

rat mlc-2 gene examples taught in the specification. The declaration further points to Example 11 of the instant specification for the superior efficiency of the Ad-mlcLuc for cardiac specific gene expression over another muscle derived promoter, the Ad-mhcLu (alpha-mhc) from the same Ad vector. Applicant states that significant non-specific expression and significantly lower expression was obtained with the alpha-mhc promoter versus the Ad-mlc-Luc construct. Applicant argues that "said experimental evidence supports my point of view that a skilled reader of the present specification will in fact be able to practice, without the need of "trial and error" experimentation, the invention within the scope of the claimed recombinant vectors, carrying a regulatory mlc-2 gene fragment which must be functional, ie. directs cardiac specific gene expression."

However, as argued in the previous Action, several unpredictable issues remain with regard to the scope of the instant claims. In the face of the unpredictability in the art taught (1) in the Franz et al. (Card Res. 35 (1997), pages 564-565 especially) for expression of any muscle specific tissue specific expression *in vivo*, (2) in the abstracts disclosed in the Amendment received 12/4/01 for cardiac-specific tissue expression by other cardiac promoters, and (3) the general unpredictability in the field of somatic gene transfer *in vivo* for design of functional vectors as taught by Anderson (argued previously) and by Reynolds et al. (Molecular Medicine Today, 1/99, pages 25-30), one skilled in the art would still not be enabled to make and use the scope of viral vectors claimed and by any route of administration claimed (since claim 69 was amended to remove the limitation that delivery is by direct injection in to the cardiac muscle).

The pointing to the entire promoter region of both human and rat, does not further clarify the portions necessary for the cardiac specific expression *in vivo*. One example of the ambiguity as to which regions are necessary to produce the data demonstrated by Dr. Franz in the interview Nov. 16, 2001, but not made of record in the specification up to this point, the specification on page 3, states that the CSS sequence is necessary for mlc promoter function on page 5 of the specification that "it is also preferable the nucleic acid working model of the invention contain additionally the heart specific sequence CSS." However, on page 4 of the specification, the "region from approximately +18 to -19 up to approximately -800 with respect tot he transcription starting point of MLC2 gene of the heart is particularly preferred (see Fig. 10), since it was particularly surprising that approximately 800 bases pairs upstream of the transcription starting point were sufficient to effect a heart-specific, and particularly a hear chamber-specific, expression in an *in vivo* application, even though this sequence does not contain the so-called heart-specific sequence CSS." Without specific guidance in the art and/or from the specification as filed as to which exact sequences are responsible for the unexpected results, it remains unclear how to make and use the broad scope of viral vectors and methods of use claimed by any route of administration, one skilled in the art would necessarily practice an undue amount of experimentation to make and use the claimed invention.

Response to Arguments

Applicant states on page 4 of the response that "the Examiner is reminded that the previously pending claims 53, 55, 57, 58, 59 and 78 recite structural limitations, i.e. specific

portions of the Mlc-2 promoter that confer cardiac tissue-specific expression...." However, the same questions remain for these claims as discussed above: the actual role of the individual components in the unexpected success argued by Applicant. Further, these claims depend on claim 52 which does not take into account the unexpected vector component results argued by Applicant.

Applicant further argues on pages 5-14 that the Examiner has not provided a sufficient *prima facie* case of lack of enablement under the guidelines of *In re Wands*. Applicant states on page 6 that "the Examiner improperly relies entirely upon the unpredictability factor in making the instant rejection."

In response, the previous Official Action argued both the quantity of experimentation necessary (the types of "trial and error" experimentation), the amount of direction or guidance provided by Applicant's declaration and interview over that provided in the specification, the presence of working examples also provided by the declaration and interview in view of the specification, the nature of the invention as a gene therapy invention, and the state of the prior art and relative skill of those in the art for gene therapy with viral vectors *in vivo* as unpredictable (the references cited were Anderson and Reynolds et al.) in view of the claimed invention. Therefore, although the individual factors for the *Wands* analysis were not explicitly stated, the components were all considered and weighed and are apparent from the analysis of the claimed invention in view of the high level of unpredictability in the art for the type of invention claimed, methods of gene therapy.

Applicant makes several assumptions on pages 7 and 8 that the quantity of experimentation to make and use the claimed invention is trivial. However, Applicant does not account for the breath of the claims drawn to administration *in vivo* to any human, the results of which are not predictable based on the teachings of Anderson and Reynolds dealing with the chronic problems of gene therapy, design of vectors and administration for the desired therapeutic effect. On pages 8 and 9 of the response, Applicant states that the specification provides "what DNA is likely useful for providing cardiac-specific expression." So far, the exact regions necessary are not clearly described, however, and the invitation to practice further basic research to demonstrate the exact regions necessary not considered proper guidance for how to make and use the claimed invention. Although the skill of the typical artisan will have an advanced degree, the nature of the invention as a gene therapy invention remains highly unpredictable even for the most talented doctors.

3. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

4. Any inquiry concerning this communication or earlier communications from the examiner should be directed to *Mary M. Schmidt*, whose telephone number is (703) 308-4471.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *John LeGuyader*, may be reached at (703) 308-0447.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group Analyst, *Katrina Turner*, whose telephone number is (703) 305-3413.

M. M. Schmidt
September 9, 2002

SEAN McGARRY
PRIMARY EXAMINER
1635